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Reactivities of Stable Rotamers. XIV. Reaction of 9-[2-(Substituted Methyl)-6-methylphenyl]fluorene Rotamers with Butyllithium[1)]

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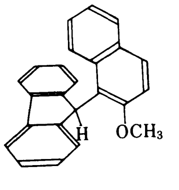
The title compounds of which substituents carry atoms with lone-pair electrons have been prepared and their rotamers isolated as stable entities at room temperature. Deprotonation rates of these rotamers with butyllithium in benzene-hexane solution show a striking difference depending upon the substituents and the rotamers. In both *sp* and *ap* series, compounds with a methoxyl group exhibit the largest rate constants, while those with a sulfur substituent show the smallest reactivity. The difference is explained in terms of coordination ability of the heteroatoms toward butyllithium and by taking advantage of the entropy effect at the transition state of lithiation. The difference in reactivities between rotamers is further striking in a sense that the reactions differ in the order; *sp* rotamers show the first-order kinetics while *ap* rotamers obey the second-order kinetics in the substrate. By assuming that the observed rates are the sum of the first-order and the second-order contributions, we estimate the minimum ratios of the first-order rate constants between *sp* and *ap* rotamers, k_1^{sp}/k_1^{ap}, to be >2300 in the methoxyl and dimethylamino derivatives and >240 in the methylthio derivatives.

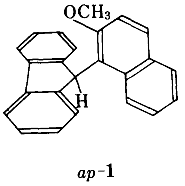
Understanding of the reactivities of rotational isomers is essential for the improvement of selectivity of a reaction. The estimation of the intrinsic reactivity of a rotamer is, however, hampered by the fact that the fast interconversion among rotamers takes place. Some years ago, we were able to isolate stable rotamers of 9-arylfluorene derivatives at room temperature[2)] and have made it possible to investigate the reactivities of rotational isomers.

Fluorene is an acidic compound because, if it is derpotonated at the 9-position, the 6 π electron system develops which should be stabilized due to the aromaticity.[3)] Thus we first selected the deprotonation of 9-arylfluorene derivatives when we launched the project of the work on reactivity of conformational isomers.

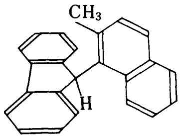
In 9-(2-methoxy-1-naphthyl)fluorene (**1**) the difference in deprotonation rates between the *sp* and *ap* rotamers reached the order of 10^3.[4)] The large difference in reactivities observed in this system attracted our attention. Thus, in a previous paper of this series, we reported the lithiation of a pair of 9-arylfluorene rotamers which consist of carbon and hydrogen only: The ratio of lithiation rates in the case of 9-(2-methyl-1-naphthyl)fluorene (**2**) was only 7.0 in favor of the *sp* form. The difference can solely be ascribed to the steric effects.[5)] Thus the large difference in lithiation rates in the rotamers of **1** must be ascribed to the existence of the coordinating methoxyl group in a suitable position.



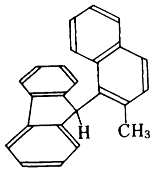
sp-**1**



ap-**1**

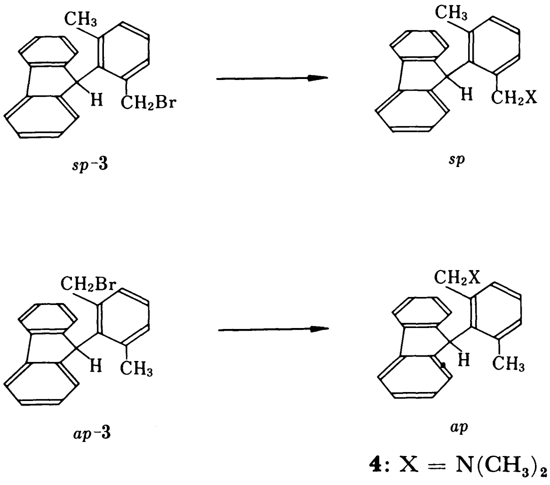


sp-**2**



ap-**2**

Then it became of interest to see whether a hetero atom located remotely from the site of the deprotonation can assist the reaction. Thus in order to investigate the effect of the heteroatoms, we have prepared 9-[2-(substituted methyl)-6-methylphenyl]fluorene derivatives. *sp*-Rotamers of compounds **4**, **5**, and **6** were prepared by the nucleophilic substitution reactions of *sp*-**3** with dimethylamine, methanol, or sodium methanethiolate, respectively. *ap*-Rotamers were also prepared from *ap*-**3** in a similar way.



4: X = $N(CH_3)_2$
5: X = OCH_3
6: X = SCH_3

In this paper, we wish to report and to discuss the results on deprotonation rates of these rotamers, which showed striking differences from a rotamer to another.

Experimental

9-[2-(Dimethylaminomethyl)-6-methylphenyl]fluorene (4). To a solution of 320 mg of *sp*-**3**[6] in 50 mL of tetrahydrofuran was added 10 mL of 50% aqueous dimethylamine. The mixture was stirred at room temperature for 3 h and then the solvents were evaporated *in vacuo*. The residue was dissolved in 20 mL of ether and dried over sodium sulfate. After evaporation of the solvent, the residue was submitted to silica-gel TLC. Elution with dichloromethane–ethanol (10:1) gave 208 mg (72%) of *sp*-**4**. Recrystallization from hexane–tetrahydrofuran afforded a pure material, mp 87—88 °C. Found: C, 87.89; H, 7.33; N, 4.30%. Calcd for $C_{23}H_{23}N$: C, 88.13; H, 7.40; N, 4.47%. ^{1}H NMR(CDCl$_3$) δ=1.10 (3H, s), 2.32 (6H, s), 3.69 (2H, s), 6.02 (1H, s), 6.8—7.5 (9H, m), 7.7—7.9 (2H, m).

To a solution of 130 mg (0.37 mmol) of *ap*-**3** in 50 mL of benzene was added 5 mL of aqueous dimethylamine and 120 mg (0.58 mmol) of silver perchlorate. The mixture was stirred for 20 h at room temperature and then the organic layer was separated. After drying over sodium sulfate, the solvent was evaporated and the residue was submitted to silica-gel TLC (dichloromethane–ethanol (10:1)) to give 52 mg or 44% of *ap*-**4**, mp 90—91 °C, as colorless crystals. Found: C, 87.83; H, 7.15; N, 4.47%. Calcd for $C_{23}H_{23}N$: C, 88.13, H, 7.40; N, 4.47%. ^{1}H NMR (CDCl$_3$) δ=1.51 (6H, s), 2.11 (2H, s), 2.70 (3H, s), 5.44 (1H, s), 7.2—7.5 (9H, m), 7.7—7.9 (2H, m).

9-(2-Methoxymethyl-6-methylphenyl)fluorene (5). Both *sp* and *ap* rotamers were obtained by the treatment of *sp*-**3** and *ap*-**3** with methanol, respectively, as reported previously.[6] mp: *sp* 65—67 °C; *ap* 118 °C.

9-[2-(Methylthiomethyl)-6-methylphenyl]fluorene (6). To a solution of 253 mg (0.72 mmol) of *sp*-**3** in 50 mL of tetrahydrofuran was added 5 mL (11 mmol) of *ca.* 15% aqueous sodium methanethiolate. The mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was dissolved in 20 mL of ether and the solution was dried over sodium sulfate. The ether was evaporated and the resulting oil was submitted to silica-gel TLC. Elution with benzene-hexane (1:1) gave 203 mg (88%) of *sp*-**6**, mp 66—67 °C, as colorless crystals. Found: C, 83.39; H, 6.09; S, 10.41%. Calcd for $C_{22}H_{20}S$: C, 83.50; H, 6.37; S, 10.13%. ^{1}H NMR (CDCl$_3$) δ=1.08 (3H, s), 2.12 (3H, s), 4.00 (2H, s), 5.63 (1H, s), 6.7—7.6 (9H, m), 7.7—7.9 (2H, m).

The *ap*-rotamer of **6** was similarly prepared from *ap*-**3** and sodium methanethiolate in tetrahydrofuran–water solution in 80% yield and was obtained as colorless crystals, mp 76—79 °C. Found: C, 83.52; H, 6.28; S, 10.04%. Calcd for $C_{22}H_{20}S$: C, 83.50; H, 6.37; S, 10.13%. ^{1}H NMR (CDCl$_3$) δ=1.28 (3H, s), 2.45 (2H, s), 2.67 (3H, s), 5.47 (1H, s), 6.7—7.5 (9H, m), 7.7—7.9 (2H, m).

Kinetic Measurement. Following is a typical procedure. A solution of 99.9 mg of *sp*-**4** in 900 µL of benzene-d_6 was prepared. By the use of a microsyringe, 200 µL of this solution (7.08×10^{-5} mol of the substrate) was taken into an NMR sample tube. To each of the 4 samples thus prepared, 300 µL of *ca.* 15% butyllithium in hexane solution was added at −78 °C under a nitrogen atmosphere. These samples were gradually warmed with stirring to make homogeneous solutions. The quantity of butyllithium was determined to be 7.1×10^{-4} mol from the integrated intensity of the signal due to methylene protons alpha to lithium in ^{1}H NMR spectra. Thus the concentration of butyllithium was found to be 10 times as much as that of the substrate. The rates of reactions were determined by monitoring the proton signals due to 4-H and 5-H of the fluorene ring. These protons gave a multiplet signal at δ 8.0—8.2 in the lithiated compound. In each set of the data obtained at 4 different temperatures, a plot of log $(1-x/a)$ *vs.* t gave a good straight line, where a is the initial amount of the substrate and x the amount of the product at time t. The pseudo-first-order rate constants were then obtained by the usual way.

The deprotonation reactions of the other rotamers also obeyed the pseudo-first-order kinetics. The rate constants were similarly obtained at 4 different temperatures. By putting these rate constants into Eyring equation, we obtained the activation parameters for lithiation.

The rates of reactions in the *ap*-rotamers could be followed as in the cases of the *sp*-rotamers. In these cases, however, the treatment of the data assuming the pseudo-first-order kinetics did not give a straight line, but that assuming the rates of second order in the substrate did a straight line.

In all of these reactions, the initial amount of butyllithium was kept constant at 7.1×10^{-4} mol. The reaction temperatures were determined from the difference in chemical shifts between the OH and the methyl signals of methanol in ^{1}H NMR spectra.

Results and Discussion

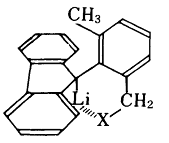
Rotational Barriers and Rates of Lithiation. Barriers to rotation about C_9–C_{aryl} bond in compounds **4**, **5**, and **6** are expected to be similar to that of compound **3** for the process *sp*→*ap*, since the effect of substituent X in the types, $-CH_2X$,[7] $-COX$,[8] and $-OCOX$,[9] on the barrier to rotation is known to be negligible in the 9-arylfluorene system regardless of the kinds of the substituent X. The barrier to rotation for the process *ap*→*sp* can vary especially when attractive or repulsive interactions are present in the *ap* form between X and fluorene ring.[8,9] Since such effects are not expected in the *ap* forms of the compounds examined in this work, the barriers to rotation are estimated to be $E_a=27.1\pm1.0$ kcal mol^{-1} (1 cal=4.18 J) or $\Delta G^{\neq}=28.0\pm1.0$ kcal mol^{-1} at 31.5 °C on the basis of the results reported for compound **3**.

If we take the minimum values of the barrier to rotation, 27 kcal mol^{-1}, the rate constants of interconversion, k_1 and k_{-1}, are calculated to be 3.3×10^{-7} s^{-1}. Since the pseudo-first-order rate constant of lithiation is at least 2×10^{-4} s^{-1} (*sp*-**6**) at 31.5 °C, isomerization of the *sp* rotamer to the *ap* during the lithiation needs not be considered. In the case of *ap* rotamers, however, the rate of isomerization of the *ap* to the *sp* isomer and that of lithiation are comparable and are not very much different from each other especially in the case of *ap*-**6**: the initial rate of lithiation is given by $k^{ap}[ap]_0^2=8.0\times10^{-8}$ mol L^{-1} s^{-1}, which is only 2.4 times larger than the isomerization rate, $k_{-1}[ap]_0=3.3\times10^{-8}$ mol L^{-1} s^{-1}, if the concentration of the substrate is 0.10 mol L^{-1}. Therefore, partial isomerization of *ap*-**6** to *sp*-**6** may take place under the conditions, which will be followed by the fast lithiation to the product. Raising the temperature increases both k_{-1} and k^{ap}, making the analysis difficult. Thus the rates of lithiation were measured at 31.5 °C only.

$$\begin{tikzcd}
sp \arrow[r, shift left, "k_1"] \arrow[d, "k^{sp}"'] & ap \arrow[l, shift left, "k_{-1}"] \arrow[d, "k^{ap}"] \\
sp\text{-P} & ap\text{-P} \arrow[l]
\end{tikzcd}$$

Structure of Lithiated Product. Both *sp* and *ap* rotamers gave identical spectra by lithiation. The structure of the lithiated compound is thought to be **7** where the heteroatom can coordinate to lithium at position 9 to stabilize this form. Such a stabilization is not expected in **8** because of the unfavorable distance between the methoxyl oxygen and the lithium. A piece of experimental evidence supporting this structure is the chemical shifts of the methylene and methyl protons which are connected to the heteroatom. In the lithiated compound derived from **5**, methylene and methyl protons gave broad signals at δ 4.6 and 3.0, respectively, in benzene–hexane (2:3) solutions. These chemical shifts resemble those of the corresponding protons of *sp*-**5**, δ 4.6 and 3.1, in the same solvent system but differ greatly from these of *ap*-**5**, δ 3.3 and 2.6. The results suggest that the methylene and methyl groups in question are located nearly in the plane of the fluorene ring. Although we failed to detect the methyl signals in the NMR spectra of lithiated compounds derived from **4** and **6** owing to the interference of the huge peaks due to solvents, we could find the methylene signals appearing at similar positions as those of the starting *sp* rotamers.

Another piece of evidence for the structure of the lithiated product came from the quenching experiment of it with hydrochloric acid at 0 °C. After the work up procedure as usual, ^{1}H NMR spectrum showed the formation of the *sp* rotamer as a sole product. Since it is well known that the electrophilic substitution of lithiated compounds in nonpolar solvents such as benzene or hexane proceeds with retention of configuration,10) the formation of the *sp* rotamer is the direct indication that **7** is the correct structure for the product.



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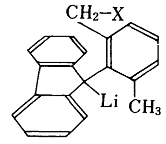

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It is difficult to assume that the lithiated structure **7** is directly formed from the *ap* isomers. Instead, the structure **8** will be formed at the first stage and will isomerize to **7** because of the thermal stability of **7**. The barrier to isomerization is expected not prohibitively high in rotation mechanism: The barrier to rotation is known to be reduced as a bulky substituent is introduced to the 9-position of 9-arylfluorenes.11)

TABLE 1. PSEUDO-FIRST-ORDER RATE CONSTANTS ($\times 10^4$ s^{-1}) OF LITHIATION WITH TEMPERATURE (°C) IN PARENTHESES OF *sp* ROTAMERS[a]

sp-**4**	1.95 (−20.5), 2.93 (−16.2), 12.0 (0.7), 18.8 (4.8)
sp-**5**	1.50 (−24.0), 2.37 (−19.3), 4.96 (−13.7), 7.97 (−9.0)
sp-**6**	2.28 (32.8), 3.29 (37.0), 5.94 (42.6), 10.5 (48.6)

a) Initial concentrations of butyllithium and the substrate were 1.42 and 0.14 mol L^{-1}, respectively.

TABLE 2. ACTIVATION PARAMETERS FOR LITHIATION OF *sp* ROTAMERS

Compound	$\Delta H^{\neq}$	$\Delta S^{\neq}$
	kcal mol^{-1}	e. u.
sp-**4**	11.7±1.1	−28.9±4.3
sp-**5**	14.6±0.9	−17.1±3.4
sp-**6**	18.5±1.6	−14.8±5.1

a) 1 e.u.=4.18 J K^{-1} mol^{-1}.

Kinetics. Deprotonation reactions were carried out by the addition of a hexane solution of butyllithium into a benzene solution of the substrate. The reaction rates were followed by monitoring ^{1}H NMR signals at low fields. The starting material possessed a multiplet signal at δ 7.7—7.9 due to 4-H and 5-H of the fluorene ring, whereas the product exhibited a doublet signal at δ 8.0—8.2, thanks to the aromatic character of the product anion.

Analysis of the data for the *sp* series of compounds conformed with the pseudo-first-order kinetics. In Table 1 are listed the pseudo-first-order rate constants thus obtained. Putting these rate constants into the Eyring equation afforded the activation parameters for the reaction, which are shown in Table 2.

By contrast, for the *ap*-rotamers, the reaction rates did not obey the pseudo-first-order kinetics but were second order in the substrate. The second order kinetics in the substrate was further confirmed by the change in the initial concentration. Thus the half-life of *ap*-**5** became longer when the less amount of the substrate was used than the original case. Since the rates of lithiation of *ap*-rotamers were very low even at ambient temperature in the concentration range examined, measurement of the rates at higher temperatures is required to obtain the activation parameters. Raising the temperature, however, may cause the isomerization of the *ap* rotamer to the *sp* which will be deprotonated rapidly. Thus the pseudo-second order rate constants were obtained at 31.5 °C only which are listed in Table 3 together with the concentration of the substrates and the relative rates.

Reaction Mechanisms. Before discussing the difference in reactivities among compounds or between rotamers, the reaction mechanisms of each rotamer

Table 3. Pseudo-second-order rate constants of lithiation of *ap* rotamers at 31.5 °C and related data[a)]

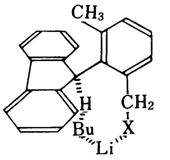
Compound	Rate Constants $mol^{-1}\,L\,s^{-1}$	Concentration $mol\,L^{-1}$	Relative Rates
ap-**4**	5.34×10^{-5}	0.10	6.7
ap-**5**	3.20×10^{-4}	0.051	40
	3.38×10^{-4}	0.084	42
ap-**6**	7.98×10^{-6}	0.10	1.0

a) Initial concentration of butyllithium was 1.42 mol L^{-1}.

must be considered. In nonpolar solvents, such as benzene or cyclohexane, butyllithium exists as a hexamer[12)] and carbon–lithium bond is mainly covalent. As a result, butyllithium behaves as a bulky reagent. In more polar solvents than hydrocarbons, such as ether or tetrahydrofuran, however, coordination of solvent molecules toward lithium occurs to result in the deaggregation of butyllithium.[12,13)] The deaggregation together with the increase in ionic nature of the carbon–lithium bond in the polar solvents makes butyllithium a more reactive species. In fact, a parent hydrocarbon, 9-(2,6-xylyl)fluorene, did not react with butyllithium at 31.5 °C in a benzene–hexane solution even after several days, while it did react instantaneously in tetrahydrofuran solutions at the same temperature.[5)] Thus the reaction of *sp* and *ap* rotamers with butyllithium, which occured even in nonpolar solvents is ascribed to the coordination effect of the substituent to the butyllithium and the reaction mechanism must be considered accordingly.

The large negative values of entropy of activation for the reactions of the *sp* series shown in Table 2 suggest that the reactions proceed at least bimolecularly. Deaggregation of butyllithium will take place, when the substrate and butyllithium collide, to form an active species responsible for deprotonation by the assistance of the heteroatom in the substituent. There may be several active species, which differ in the degree of aggregation and are differently contributing to the total reaction. In the second step, the active species deprotonates from the 9-position of the same complex. A plausible structure of the transition state is given by **9** in the case where butyllithium exists as a monomer.

In the case of *ap* rotamers, the reaction path must be different from that of *sp* rotamers because the rates of deprotonation of the *ap* rotamers obeyed the second-order rate law in the substrate. Thus the direct abstraction of 9-H by butyllithium spanning between the substituent and the 9-H as shown by **10** is neglected, since the rate should be first order in the substrate, if it were the case. Inspection of the molecular model also revealed that the distance between the coordinating butyllithium and the 9-H is unfavorable for the reaction to occur, especially when the butyllithium is a monomer. It is, therefore, more reasonable to consider an intermolecular reaction: Coordinated butyllithium abstracts the 9-H of another molecule in the rate-determining step.



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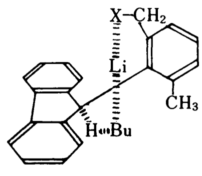

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Comparison of Reactivities among Compounds. a) sp-*Rotamers*: As discussed in the previous section, coordination of the substituent to lithium is very important for the reaction to occur. Then the rate of the reaction of the *sp* rotamer is affected both by the rate constant of deprotonation and the equilibrium constant of deaggregation. If a strong coordination of the heteroatom toward the aggregated butyllithium takes place, it will increase the concentration of active species as well as the ionic character of the lithium–carbon bond: It results in the increase in the rate of deprotonation as well as the equilibrium constant. It is, therefore, reasonable to state that the compound which has a substituent of stronger coordinating ability to lithium ion is much more reactive than the compound carrying a less coordinating substituent.

The rate constants in Table 1 indicate that the oxygen-containing **5** showed the highest reactivity toward butyllithium among the compounds examined at ambient temperature. Nitrogen substitution similarly accelerated the reaction but the sulfur substitution was not so effective as those of the former two compounds. The high reactivities observed in *sp*-**4** and *sp*-**5** relative to that in *sp*-**6** seem to correspond to the generally accepted coordination ability of the heteroatoms concerned toward lithium ions: lithium ions are classified as a typical hard acid[14)] and thus tend to make a stronger bond with a hard base such as a nitrogen- or oxygen-containing substituent than a soft base such as a sulfur-containing group.

The recent thermodynamic study by Xu and Smid showed that polyamines such as penta-*N*-methyldiethylenetriamine and hexa-*N*-methyltriethylenetetramine have a higher affinity toward lithium ions than the corresponding oxygen analogs, di- and triethylene glycol dimethyl ether, respectively.[15)] These results suggest that the nitrogen-containing substituent has a stronger coordination ability toward lithium ions than the oxygen-containing group and thus are against the order of the reactivities that we observed.

Further inspection of the data in Table 2, however, reveals that *sp*-**4** has the smallest activation enthalpy and the largest negative value of entropy of activation among the compounds examined. The former is ascribed to the strong coordination of the dimethylamino group to butyllithium in the transition state of reaction, being consistent with the thermodynamic data. The latter could be explained in terms of the orientation of the reactants required in the transition state. Since a dimethylamino group has only one lone pair of electrons, the direction of the lone-pair electrons is important for the effective coordination. Existence of two methyl groups also prohibits certain conformations for steric reasons. As a result, only a limited number of conformations is possible for the dimethylamino group to coordinate to butyllithium. These factors are considered to decrease the entropy of activation. In the case of *sp*-**5**, such a restriction of conformations may not be severe since the methoxyl group has two pairs of electrons and only one methyl group. Thus the apparent reversal in the order of reactivities between **4** and **5** is ascribed to the entropy effect. The activation parameters in Table 2 suggest that the rate constants of *sp*-**4** become larger than those of *sp*-**5** at temperature below −28 °C, where the molecular motion slows down and the rates are controlled mainly by the enthalpy of activation.

b) ap-Rotamers. Reactivities of *ap* rotamers are quite similar to those of *sp* rotamers in a sense that *ap*-**5** and *ap*-**6** showed the largest and smallest rate constants, respectively, among the compounds examined at 31.5 °C. The data in Table 3 also showed that the ratio of rate constants, $k(ap\text{-}\mathbf{5})/k(ap\text{-}\mathbf{4})$, is *ca.* 6.0 which is twice as large as the corresponding ratio in the *sp* series. The difference in the ratio can be explained in terms of the entropy effect as well. The number of conformations possible for the *ap*-form of **4** is more limited than *sp*-**4** because of the presence of the fluorene ring in proximity. As to the C(aryl)-to-C_α(substituent) bond rotation, no conformation is possible in which the C–N bond directs toward the fluorene ring. In addition, any invertomers about the nitrogen atom, in which one or two of the methyl groups directs toward the fluorene moiety may be unstable for the steric reasons. These factors all act to decrease the entropy when lithium ions coordinate to the amino-nitrogen.

Comparison of Reactivities between Rotamers. The most striking feature in the reactivities of rotamers is that they showed different mechanism in the lithiation. Thus the direct comparison of the rate constants between *sp* and *ap* rotamers may be meaningless. For the comparison, let us assume that the observed rate is given by the sum of the first-order and the second-order contributions as described by equations 1 and 2 for the cases of *sp* and *ap* series, respectively. Although it is possible to state that various kinds of reactions, those of butyllithiums of different degrees of aggregation and those of the higher order than the second, can take place, as a rule of thumb, the assumption may be justified.

$$\mathrm{Rate}(sp) = k_1^{sp}[sp] + k_2^{sp}[sp]^2 \quad (1)$$

$$\mathrm{Rate}(ap) = k_1^{ap}[ap] + k_2^{ap}[ap]^2 \quad (2)$$

Table 4. Pseudo-first-order rate constants of *sp* and *ap* rotamers at 31.5 °C

Compound	k_1^{sp} / s^{-1}	k_1^{ap} / s^{-1}	k_1^{sp}/k_1^{ap}
4	1.25×10^{-2}	$<5.3\times10^{-6}$	>2300
5	3.80×10^{-2}	$<1.6\times10^{-5}$	>2300
6	1.95×10^{-4}	$<8.0\times10^{-7}$	>240

where k_1 and k_2 are rate constants of first and second order reactions in the substrate, respectively.

In these equations, the concentration of butyllithium is included in the constants, k_1 and k_2, since it is at least 10 times as much as the concentration of the substrate. In the case of *sp* rotamers, the observed rate obeyed the first-order kinetics, meaning that the first term predominates over the second term in Eq. 1. In the case of *ap* rotamers, in contrast, second term becomes predominant in Eq. 2. Thus we concluded the following two relations, 3 and 4:

$$k_1^{sp} \gg k_2^{sp}[sp] \quad (3)$$

$$k_1^{ap} \ll k_2^{ap}[ap] \quad (4)$$

By considering the data in Table 2 with respect to these relations, we can calculate the maximum values of k_1^{ap} for each *ap* rotamer. In Table 4 are listed these values together with the rate constants of the reaction of the *ap* form at 31.5 °C and the minimum ratios of k_1^{sp}/k_1^{ap}.

It may be possible to obtain the intrinsic k_1 values for *ap* rotamers by measuring the rates at the low concentration range of the substrates, where the second term of Eq. 2 is negligibly small. Present method, which consists of the monitoring of the signals by ^{1}H NMR spectroscopy, however, makes it very difficult to obtain reasonably good results in such a low concentration range. In addition, the reaction of the *ap* form under such conditions may be too slow to be practicable for the measurement, even if we assume that a suitable methodology is found.

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